Electronic Supplementary Material

What's New in Intensive Care?

Should we rely on trials with Disease- rather than Patient-oriented Endpoints?

Harm-Jan de Grooth, Jean-Jacques Parienti, Heleen M. Oudemans-van Straaten

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Methods

To analyze the evolution of primary endpoints in ICU research over the past 15 years, we performed a comprehensive search to identify all RCTs with critically ill patients published in the years 2001, 2006, 2011 and 2016 in 5 major critical care journals (Intensive Care Medicine, The American Journal of Respiratory and Critical Care Medicine, Critical Care Medicine, Critical Care, Chest) and 3 high-impact medical journals (The New England Journal of Medicine, The Lancet and The Journal of the American Medical Association). For each trial, we recorded the sample size, the primary endpoint and the p-value of the primary endpoint. Patient-oriented primary endpoints were defined as any measure of mortality, functional outcome or quality of life at follow-up. Disease-oriented primary endpoints included all other outcomes.

Inclusion- and exclusion criteria

Inclusion criteria:

- Parallel group randomized controlled trials with patients admitted to the intensive care unit or with patients expected to be admitted to the intensive care unit.

Exclusion criteria

- Secondary analyses of previously published trials.
- Crossover trials (no patient-oriented between-group comparison possible).
- No specifically defined primary endpoint.

Search strategy

PubMed was queried on February 1, 2017 using two separate searches. With search #1 (specified below) we searched for all reports with a mention of randomization in 5 Intensive Care focused journals. With search #2 (specified below) we searched for all reports with a mention of randomization and Intensive Care related terminology in 3 high-impact general-interest journals. The results of the two queries were then combined.

Search # 1:

("Intensive care medicine"[Journal] OR
"Am J Respir Crit Care Med"[Journal] OR
"Chest"[Journal] OR
"Critical care medicine"[Journal] OR
"Critical care (London, England)"[Journal])
AND
random*

Date filter: January 1 to December 31 of the years 2001, 2006, 2011 and 2016.

Search # 2:

(
"N Engl J Med"[Journal] OR
"Lancet"[Journal] OR
"JAMA"[Journal]
)
AND
(
"Critical Care"[Mesh] OR "intensive care" OR "ICU" OR
"Critical Illness"[Mesh] OR "critically ill" OR "critical illness" OR
"severe sepsis" OR "septic shock" OR "shock"[Mesh] OR
"cardiac arrest" OR
"ARDS" OR "acute respiratory distress syndrome" OR
"Respiration, Artificial"[Mesh] OR "ventilation" OR "ventilated" OR
"hemofiltration" OR "haemofiltration" OR "extracorporeal"
)
AND
random*

Date filter: January 1 to December 31 of the years 2001, 2006, 2011 and 2016.

Collected data and statistical analyses

For each randomized controlled trial, we recorded the year of publication, the total sample size, the primary endpoint and the p-value of the primary endpoint. The primary endpoint was categorized as 'patient-oriented' or as 'disease-oriented. Patient-oriented primary endpoints were defined as any measure of mortality, functional outcome or quality of life at follow-up. Disease-oriented primary endpoints included all other outcomes, both clinical and biomarker-based.

For each endpoint category, we tested the trend over time using Poisson regression, with the number of trials reporting an endpoint as dependent variable and the publication year as independent variable. This trend test was repeated for the subset of trials with a sample size larger than 200 and in the subset of trials published in the three high-impact journals.

Reported p-values were compared between endpoint categories using the Wilcoxon rank-sum test. The relative proportion of 'positive' trials (those that report a primary p-value < 0.05) was compared using Fisher's exact test.

Search results and baseline characteristics

Search results

1604 Results from PubMed query

1177 Not relevant (by title or article type)

427 Studies assessed for eligibility

174 Trials excluded based on trial design

69 Not a randomized controlled trial

63 Did not report a specifically defined primary endpoint

31 Secondary analyses of previously published trial

11 Crossover randomized trials

253 Trials included in analysis

Baseline characteristics and additional results

Table 1 Number of trials per endpoint category per year and median sample sizes.

		Number of trials		
		Patient-oriented endpoints	Disease-oriented endpoints	Median sample size (IQR)
2001	All trials	10	43	60 (30-200)
	Critical care journals	3	38	44 (23-90)
	High Impact medical journals	7	5	276 (182-615)
	Sample size > 200	9	4	304 (263-1342)
2006	All trials	19	52	136 (70-370)
	Critical care journals	9	47	108 (44-241)
	High Impact medical journals	10	5	740 (247-1000)
	Sample size > 200	13	14	600 (318-766)
2011	All trials	9	50	150 (60-341)
	Critical care journals	4	44	128 (60-209)
	High Impact medical journals	5	6	3141 (246-4202)
	Sample size > 200	7	17	611 (261-2210)
2016	All trials	12	58	200 (101-381)
	Critical care journals	4	39	129 (71-200)
	High Impact medical journals	8	19	408 (292-612)
	Sample size > 200	9	24	386 (293-604)

A total of 253 eligible trials were identified. From 2001 to 2016, disease-oriented primary endpoints became progressively more prevalent, specifically in the subset of trials with sample sizes of more than 200 patients (figure 1-A, p=0.0004 for trend) and in trials published in high-impact journals (p=0.0017 for trend). For trials with a sample size of more than 500 patients, 2016 was the first year that disease-oriented endpoints were more prevalent than patient-oriented endpoints. There was no trend in the prevalence of patient-oriented endpoints (p=0.80), neither among trials with a sample size of more than 200 patients (p=0.66) nor among trials published in high-impact journals (p=0.87).

Trials with a disease-oriented endpoint reported lower primary endpoint p-values (fig. 1-C) and consequently reported more 'positive' results ($p<0.05$) than trials with a patient-oriented endpoint (57% vs. 27% of trials, p=0.0004).